AMENDMENTS TO THE SPECIFICATION

Please amend the specification as follows:

At page 1, line 1, please insert the following:

This application is a continuation application of U.S. Patent Application No.: 09/663,481 filed on September 15, 2000, now abandoned, which claims the benefit of U.S. Provisional Application No. 60/177,326, filed on January 20, 2000. This application claims priority under 35 U.S.C. §120 on U.S. Patent Application No.: 09/663,481, filed on September 15, 2000 and Provisional Patent Application No.: 60/177,326, filed on January 20, 2000. Priority is also claimed under 35 U.S.C. §119 on Great Britain Patent Application No.: 9922125.1, filed on September 17, 1999.

At page 3, line 34, please insert the following Brief Description of the Figures:

Brief Description of the Figures

FIG. 1 presents a multiple sequence alignment of the PDE1 gene family.

FIG. 2 presents an image of a Java Applet for PDE sequences.

FIG. 3 presents schematic diagrams of PDE1A subtypes for bovine, human and murine species cDNAs.

FIGS. 4A to 4D presents a Clustalus alignment of the differential N-terminal regions of PDE1A and PDE1B splice variants.

FIG. 5 presents an image of comparative Northern Blot analysis of PDE1A and PDE1B alternate splice variants with notation of the tissue source of the mRNA in the legend.

At page 5, please replace paragraph 1 as follows:

According to one aspect of the present invention there is provided an amino acid sequence comprising the sequence presented as ~~SEQ ID No. 1~~SEQ ID NO:1, or a variant, homologue, fragment or derivative thereof, wherein the amino acid sequence is capable of displaying PDE activity.

At page 6, please replace paragraphs 4 and 5 as follows:

For ~~SEQ ID No. 1~~SEQ ID NO:1 any one or more of the amino acids may be an analogue thereof.

The term "analogue" as used herein means a sequence having a sequence similar to that of ~~SEQ ID No. 1~~ SEQ ID NO:1 but wherein non-detrimental (i.e. not detrimental to enzymatic activity) amino acid substitutions or deletions have been made.

At page 7, please replace paragraph 1 as follows:

Preferably, the nucleotide sequence comprises the sequence presented as ~~SEQ ID No. 2,~~ SEQ ID NO:2, or a variant, homologue, fragment or derivative thereof, wherein the nucleotide sequence codes for an amino acid sequence that is capable of displaying PDE activity.

At page 9, please replace paragraph 1 as follows:

According to a further aspect of the present invention there is provided a nucleotide sequence selected from:

(a) the nucleotide sequence presented as ~~SEQ ID No. 2~~SEQ ID NO:2;

(b) a nucleotide sequence that is a variant, homologue, derivative or fragment of the nucleotide sequence presented as ~~SEQ ID No. 2~~ SEQ ID NO:2;

(c) a nucleotide sequence that is the complement of the nucleotide sequence set out as ~~SEQ ID No. 2~~ SEQ ID NO:2;

(d) a nucleotide sequence that is the complement of a variant, homologue, derivative or fragment of the nucleotide sequence presented as ~~SEQ ID No. 2~~ SEQ ID NO:2;

(e) a nucleotide sequence that is capable of hybridising to the nucleotide sequence set out as ~~SEQ ID No. 2~~ SEQ ID NO:2;

(f) a nucleotide sequence that is capable of hybridising to a variant, homologue, derivative or fragment of the nucleotide sequence presented as ~~SEQ ID No. 2~~ SEQ ID NO:2;

(g) a nucleotide sequence that is the complement of a nucleotide sequence that is capable of hybridising to the nucleotide sequence set out as ~~SEQ ID No. 2~~ SEQ ID NO:2;

(h) a nucleotide sequence that is the complement of a nucleotide sequence that is capable of hybridising to a variant, homologue, derivative or fragment of the nucleotide sequence presented as ~~SEQ ID No. 2~~ SEQ ID NO:2;

(i) a nucleotide sequence that is capable of hybridising to the complement of the nucleotide sequence set out as ~~SEQ ID No. 2~~ SEQ ID NO:2;

(j) a nucleotide sequence that is capable of hybridising to the complement of a variant, homologue, derivative or fragment of the nucleotide sequence presented as ~~SEQ ID No. 2~~ SEQ ID NO:2;

(k) a nucleotide sequence which is degenerate as a result of the genetic code to the nucleotides defined in (a), (b), (c), (d), (e), (f), (g), (h), (i), or (j);

(l) a nucleotide sequence comprising any one of (a), (b), (c), (d), (e), (f), (g), (h), (i), (j) and/or (k).

At page 14, please replace paragraph 6 as follows:

The terms "variant", "homologue" or "fragment" in relation to the amino acid sequence for the enzyme of the present invention include any substitution of, variation of, modification of, replacement of, deletion of or addition of one (or more) amino acid from or to the sequence providing the resultant enzyme has PDE1B2 activity, preferably being at least as biologically active as the enzyme shown in the attached sequence listings. In particular, the term "homologue" covers homology with respect to structure and/or function. With respect to sequence homology, preferably there is at least 75%, more preferably at least 85%, more preferably at least 90% homology to the sequence shown as ~~SEQ ID No. 1~~SEQ ID NO:1. More preferably there is at least 95%, more preferably at least 98%, homology to the sequence shown as ~~SEQ ID No. 1~~ SEQ ID NO:1.

At page 15, please replace paragraph 1 as follows:

Preferably, the variant, homologue or fragment of the present invention comprises a nucleotide sequence that encodes for at least 5 contiguous amino acids, preferably at least 10 contiguous amino acids, preferably at least 15 contiguous amino acids, preferably at least 20 contiguous amino acids, preferably at least 21 contiguous amino acids, preferably at least 22 contiguous amino acids, preferably at least 23 contiguous amino acids, preferably at least 24 contiguous amino acids, of the following N terminal sequence:

MANPVPVQRSHLQGPILRLRYMVK (SEQ ID NO:5)

At page 17, please replace paragraph 2 as follows:

A specific amino acid sequence of PDE1B2 is shown as ~~SEQ ID No. 1~~SEQ ID NO:1. However, the present invention encompasses amino acid sequences encoding other members from the PDE1B2 family which would include amino acid sequences having at least 60% identity (more preferably at least 75% identity) to that specific amino acid sequences.

At page 19, please replace paragraph 6 as follows:

The terms "variant", "homologue" or "fragment" in relation to the nucleotide sequence coding for the preferred enzyme of the present invention include any substitution of, variation of, modification of, replacement of, deletion of or addition of one (or more) nucleic acid from or to the sequence providing the resultant nucleotide sequence codes for or is capable of coding for an enzyme having PDE1B2 activity, preferably being at least as biologically active as the enzyme encoded by the sequences shown in the attached sequence listings. In particular, the term "homologue" covers homology with respect to structure and/or function providing the resultant nucleotide sequence codes for or is capable of coding for an enzyme having PDE1B2 activity. With respect to sequence homology, preferably there is at least 75%, more preferably at least 85%, more preferably at least 90% homology to a nucleotide sequence coding for the amino acid sequence shown as ~~SEQ ID No. 1~~ SEQ ID NO:1. More preferably there is at least 95%, more preferably at least 98% homology to a nucleotide sequence coding for the amino acid sequence shown as ~~SEQ ID No. 1~~SEQ ID NO:1. Preferably, with respect to sequence homology, preferably there is at least 75%, more preferably at least 85%, more preferably at least 90% homology to the sequence shown as ~~SEQ ID No. 2~~SEQ ID NO:2. More preferably there is at least 95%, more preferably at least 98%, homology to the sequence shown as ~~SEQ ID No. 2~~ SEQ ID NO:2.

At page 20, please replace paragraph 2 as follows:

Preferably, the variant, homologue or fragment of the present invention comprises a nucleotide sequence that encodes for at least 5 contiguous amino acids, preferably at

least 10 contiguous amino acids, preferably at least 15 contiguous amino acids, preferably at least 20 contiguous amino acids, preferably at least 21 contiguous amino acids, preferably at least 22 contiguous amino acids, preferably at least 23 contiguous amino acids, preferably at least 24 contiguous amino acids, of the following N terminal sequence:

MANPVPVQRSHLQGPILRLRYMVK (SEQ ID NO:5)

At page 29, line 10, please replace paragraph 2 as follows:

As indicated, for some applications, sequence homology (or identity) may be determined using any suitable homology algorithm, using for example default parameters. For a discussion of basic issues in similarity searching of sequence databases, see Altschul et al (1994) Nature Genetics 6:119-129. For some applications, the BLAST algorithm is employed, with parameters set to default values. The BLAST algorithm is described in detail at ~~http://www.ncbi.nih.gov/BLAST/blast_help.html~~ the NCBI web page. Advantageously, "substantial homology" when assessed by BLAST equates to sequences which match with an EXPECT value of at least about 7, preferably at least about 9 and most preferably 10 or more. The default threshold for EXPECT in BLAST searching is usually 10.

At page 73, please replace paragraph 1 as follows:

RNA master blots and multiple tissue northerns were purchased from Clontech and prehybridised for 1 hour in ExpressHyb hybridisation solution (Clontech) at 55°C. The alternatively spliced amino terminal regions were amplified by PCR using the following primer pairs:-

PDE1A3

- 5' CAG TAA CAG ATG AGC TGC 3' (SEQ ID NO:14)

and

5' GTA TTC CTT TCA GGC G 3' (SEQ ID NO:15)

to produce a 159bp fragment.

Primers for PDE1A5 (SEQ ID NO:16)

5' CAC ATT TCC TCT CTG G 3'

and

5' GGG TCT TTG GAG ATG TTT CTT CC 3' (SEQ ID NO:17)

to produce a 107bp fragment.

Primers for PDE1B1

5' CTG AGC ATG GAG CTG TCC 3' (SEQ ID NO:18)

and

5' CAG AGA CCG AAG CTT AAT CC 3' (SEQ ID NO:19)

to produce a 120bp fragment.

Primers for PBE1B2

5' CCA AAG AGG AAG TTG TCC 3' (SEQ ID NO:20)

and

5' GCA GCC TGA CAA TGG 3' (SEQ ID NO:21)

to produce a 144bp fragment.